THE SIGNIFICANCE OF GALLSTONES IN CHILDREN WITH SICKLE CELL ANEMIA

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Infection is the most common cause of high morbidity, hospitalization, and mortality in children with sickle cell anemia. In this study of pediatric sickle cell anemia patients, aged 1 to 19, we explore the hypothesis that gallstones (usually pigment stones) create a nidus of infection, predisposing the affected patients to high morbidity.

Our study involved 86 children with sickle cell anemia at the Howard University Center for Sickle Cell Disease, who had been followed at the clinic for a total of 602 patient years. Review of their records revealed that patients with gallstones had a mean number of 10.24 hospitalizations and 25.35 ambulatory visits; those without gallstones had a mean number of only 4.26 hospitalizations and 13.41 ambulatory visits.

In children with sickle cell anemia and gallstones, elective cholecystectomy (or, in the future, cholelithotripsy) could reduce the high morbidity caused by infection.

Key words • gallstones • sickle cell anemia • infection in children

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It is estimated that 16 to 20 million people in the United States have gallstones, and approximately 1 million new cases of cholelithiasis develop each year. Twenty percent of women and 8% of all men over 40 years old have gallstones.[1]

Gallstones are composed of cholesterol, calcium bilirubinate, and calcium carbonate. There are three main types of gallstones. Pure gallstones are composed almost entirely of one of these substances. Mixed gallstones consist of a mixture of these substances in varying proportions. Combined gallstones consist of combinations in which one type of gallstone forms the nucleus and another forms the shell.[2]

In the United States, about 85% of stones are composed mainly of cholesterol, and the remaining 15% are pigment stones of calcium bilirubinate.[3] The incidence of both cholesterol and pigment stones increases with age.[3-5] The risk factors associated with a higher incidence of cholesterol stones, but not pigment stones, include female gender, obesity, exogenous estrogen intake, hyperlipoproteinemia, ileal resection, total parenteral nutrition, diabetes mellitus, and primary biliary cirrhosis.[6-8] The risk factors associated with pigment stones, but not cholesterol stones, include chronic hemolysis, such as sickle cell anemia (SS), vagotomy, duodenal diverticula, and portal cirrhosis.[9-11] In 1929, a Mayo report stated that 70% of patients with congenital hemolytic anemia had associated cholelithiasis.[12]

It is well known that pigment stone formation is increased in sickle cell anemia patients.[2,13,14] Golding[14] reported the possibility that pediatric sickle cell

patients, especially those with frequent hemolytic crises, may develop cholelithiasis. Karayalcin[15] reported the incidence of cholelithiasis in pediatric sickle cell patients (4 to 18 years old) to be 17%.

Barrett-Conner et al[16] noted that infection is the most common cause of death in SS children. In their study of 166 patients, bacterial infection caused more hospitalization than other complications, representing nearly half of all hospital admissions.

Infection has been proposed as a major factor in the genesis of pigment stone formation.[3,17] Organisms such as *Escherichia coli*, *Salmonella typhosa*, and *Streptococcus faecalis* have been isolated from gallbladder walls and the centers of stones in a high percentage of cases.[18] In a study of Japanese patients by Maki,[19] hydrolysis of conjugated bilirubin by bacteria β-glucuronidase was postulated as the cause of bile pigment stones. Maki also reported a high incidence of infection in his patients with pigment stones. Indeed, the assumption that infection in pediatric patients with sickle cell anemia is a major part of the genesis of pigment stone formation is supported by studies documenting that 5% to 10% of bile obtained from patients at cholecystectomy will culture bacteria.[19]

In our study of pediatric patients with sickle cell anemia, 1 to 19 years old, we explore the hypothesis that a pigment stone, when present, is a nidus of infection by the time it is fully formed. This predisposes affected patients to higher morbidity, as measured by the number of emergency room visits and hospital admissions.

MATERIALS AND METHODS

Patient Selection

The Howard University Center for Sickle Cell Disease has one of the largest clinics in the United States. In 1986, there were 333 patients with sickle cell anemia (70.5% of the population), 105 of whom were in the pediatric age group; 100 with sickle cell-hemoglobin C disease (SC) (21.2%); 25 with sickle thalassemia (SB+) (5.3%); 5 sickle β-zero (SB^0) (1.1%); and 9 with other forms of sickle disease (1.9%). Genotype designation was made after screening and confirmation tests were performed in the hemoglobinopathy laboratories.

The criteria for selecting the study population included the availability of the patients' records for at least 1 year of follow-up and complete acute visit and hospitalization records covering the period from January 1974 to July 1987.

This retrospective study is based on the medical records of 105 sickle cell anemia patients between the ages of 1 and 19 who attended the Howard University Center for Sickle Cell Disease Clinic from January 1974 to July 1987. Group 1 consisted of sickle cell anemia patients who had a diagnosis of gallstones documented by a positive plain radiograph of the abdomen, a positive ultrasound, or an oral cholecystogram.[20] Group 2, the control group, had no documented evidence of having had gallstones. The numbers of ambulatory visits and hospital admissions were noted, with specific reference to types of infection and crises.[21-24]

The patients' medical records and diagnoses made at each ambulatory visit or hospitalization were reviewed and the frequencies of the various diagnoses obtained. We noted the number of ambulatory visits due to pharyngitis, otitis media, other upper respiratory tract problems, such as rhinorrhea, mild to moderate pain crisis, (Hand-Foot syndrome/dactylitis), epistaxis, enuresis, and other conditions, such as dermatitis, headache, and infectious mononucleosis were noted.

In the review of hospitalizations, we noted the number of hospital admissions noted for pneumonia, meningitis, osteomyelitis, general abdominal crisis, right upper quadrant pain, otitis media, severe pain crisis, including sequestration crisis, vaso-occlusive and aplastic crisis, and other conditions, such as cerebrovascular accidents, asthma, and trauma.

The relative risk (odds ratio) was estimated and used to compute the different morbidity risks in the two groups. Chi-square test was used to determine the recurrence of diagnoses made at each contact visit. Analysis of variance was used to evaluate the different variables. The regular student's *t* test was used to study whether there were significant differences in morbidity between the two groups.

RESULTS

Nineteen of the initial 105 patients did not meet the criteria for the study. Of these, 2 patients were not included in the study because they were over the age of 19; 16 were excluded because of incomplete documentation of non-Howard University clinic and hospital visits; and 1 infant was dropped because she was followed for less than a year.

The remaining 86 patients were American blacks residing in the Washington, DC area. The majority (56 patients, or 65.1%) were over 10 years of age. The total patient population was divided into two groups; group 1 consisted of 17 patients with gallstones (19.8% of the population) and group 2 consisted of 69 controls

TABLE 1. COMPARISON OF EMERGENCY VISITS IN GROUP 1 AND GROUP 2

	# of Cases	$\bar{X}$	S.D.	S.E.
Group 1	17	24.3529	19.811	4.805
Group 2	69	13.4058	8.259	0.994

Pooled Variance (EST)			Separate Variance (EST)		
F Value	Degrees of Freedom	2-Tail Prob.	F Value	Degrees of Freedom	2-Tail Prob.
3.55	84	0.001	2.23	17.39	0.039

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TABLE 2. COMPARISON OF HOSPITAL ADMISSIONS IN GROUP 1 AND GROUP 2

	# of Cases	$\bar{X}$	S.D.	S.E.
Group 1	17	10.2353	8.693	2.108
Group 2	69	4.2609	4.150	0.500

Pooled Variance (EST)			Separate Variance (EST)		
F Value	Degrees of Freedom	2-Tail Prob.	F Value	Degrees of Freedom	2-Tail Prob.
4.14	84	0.000	2.76	17.83	0.013

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(80.2% of the population). These groups were further subgrouped with reference to age and sex.

Although there were as many females as males in the general population, females represented a higher proportion of patients with gallstones (12 patients or 70.6%) compared with males (5 patients or 29.4%). Furthermore, males (55.1%) outnumbered females (44.9%) in the control group.

The mean follow-up for patients was 7.17 years. Length of follow-up did not vary significantly between the study (7.64 years) and control subjects (7.06 years).

Review of Ambulatory Visits

All 86 patients had at least two or more ambulatory visits during the study period. The mean number of visits for the study cases was 24.4, compared with 13.4 for the controls (Table 1). This represents a significant difference between the study cases and the controls ($P < .05$). Furthermore, 64.7% of the study cases had at least 15 or more ambulatory visits, but only 34.8% of the controls had as many.

Upper respiratory tract infection was a major reason for acute visits in both the study cases (82.4%) and the controls (87.0%). However, although 59.8% of the study cases had four or more acute visits for upper respiratory tract infection, only 24.6% of the controls were in this category, which points to the recurrent nature of disease in the SS child with gallstones. Group 1 had a higher incidence of pharyngitis compared with group 2, eg, 2.53 compared with 1.55.

Acute visits for mild to moderate pain crisis were recorded in 88.2% of group 1 patients and in 82.6% of group 2 patients. However, the mean number of acute visits in group 1 was 4.53 compared with 2.94 in group 2; the risk for ambulatory visits due to mild to moderate pain was 1.6 times higher in group 1 than group 2. In addition, the relative risk for epistaxis was 1.2 times higher in group 1. The mean values for visits for enuresis were 0.94 in group 1 compared with 0.33 in group 2; the mean values for other visits (ie, dermatitis, headache, infectious mononucleosis) were 7.23 for group 1 compared with 3.54 for group 2.

These results illustrate the high morbidity found in sickle cell anemia patients with gallstones.

Hospital Admissions

During the study period, all of the patients with gallstones had been admitted to the hospital at least three times. The mean number of hospital admissions in group 1 was 10.24 compared with 4.26 for group 2 (Table 2). These results are significant ($P < .05$) and support our hypothesis that children with sickle cell anemia and

TABLE 3. PATIENTS REPORTING AT LEAST ONE HOSPITAL ADMISSION

HA Diagnosis	Combined Percent	Case Group 1	Control Group 2
Pneumonia	57.0	82.4	50.7
Meningitis	4.7	5.9	4.3
Osteomyelitis	8.2	5.9	8.7
"Severe Crisis"	65.8	70.6	52.2
Otitis Media	18.6	33.5	17.4
Right Upper Quadrant Pain	9.3	35.3	2.9
General Abdominal "Crisis"	60.5	82.4	55.1

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gallstones have a higher morbidity.

At least one hospital admission for pneumonia (Table 3) was noted in 82.4% of group 1 compared with 50.7% in group 2, representing a 4.5 greater risk of hospitalization for pneumonia for patients in group 1 (Table 4). Statistical analysis of hospital admissions for pneumonia showed the results to be within the margin of significance ($\chi^2 = 5.67$, $df = 2$, $P = .06$). We recommend additional study with a larger pool of patients for a better analysis of this variable.

During this study, six patients (6.9%) were hospitalized for cerebrovascular accidents complicated by seizures. In general, these patients had a higher morbidity than other individuals in their age group. However, this is not surprising, as cerebrovascular accidents have already been reported to produce devastating complications in patients with sickle cell anemia.[25-28]

There was no significant difference in the prevalence of meningitis and osteomyelitis between study and control cases, possibly due to the low level of this diagnosis noted in this series. However, it is important to mention that our values for these two diagnoses (meningitis occurred in 4.7% and osteomyelitis occurred in 8.2%) compare favorably with the results in the literature.[29] Severe crises (ie, vaso-occlusive, aplastic, sequestration crises) were noted in 70.6% of study cases compared with 52.2% of the controls. This result represents a 2.2 times greater risk for study cases. However, recurrence of hospital admissions for these various crises was not significant ($\chi^2 = 8.92$, $df = 2$, $P = 0.1$).

Otitis media was noted in 33.5% of the study cases compared with 17.4% of control cases, resulting in only one hospital admission for a patient who was in the group with gallstones.

Right upper quadrant pain is the most important clinical manifestation of cholelithiasis. It was recorded in 35.4% of cases in group 1 but in only 2.9% of the

TABLE 4. RELATIVE RISK FOR HOSPITAL ADMISSIONS

Condition	Yes	No	Relative Risk
Pneumonia			
Cases	14 (82.4)	3 (17.6)	4.5
Controls	35 (50.7)	34 (49.3)	
	49 (57.0)	37 (43)	
"Severe Crisis"			
Cases	12 (70.6)	5 (29.4)	2.2
Controls	36 (52.2)	33 (47.8)	
"Other"			
Cases	15 (88.2)	2 (11.8)	6.9
Controls	36 (52.2)	33 (47.8)	
	51 (59.0)	35 (41.0)	
Right Upper Quadrant Pain			
Cases	6 (35.3)	11 (64.7)	18.3
Controls	2 (2.9)	67 (97.1)	
	8 (9.0)	78 (91.0)	
General Abdominal Crisis			
Cases	14 (82.4)	3 (17.6)	3.8
Controls	38 (55.1)	31 (44.9)	
	52 (60)	34 (40.0)	

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cases in group 2. Our data indicate that children with sickle cell anemia and gallstones have an 18.3 times greater risk of being hospitalized because of right upper quadrant pain than do their counterparts without gallstones. Furthermore, 5.9% of study cases had two or more hospital admissions for right upper quadrant pain compared with no admissions in the control patients ($\chi^2 = 17.42$, $df = 2$, $P < .001$).

Abdominal pain episodes, described as abdominal crises, were encountered in 82.4% of the study cases compared with 55.1% of the controls. This outcome represented a 3.8 times greater relative risk for the study cases compared with controls. Thus, the children with sickle cell anemia and gallstones were more likely to be hospitalized because of abdominal crises than their counterparts without gallstones. The study cases had a mean of 4.59 hospitalizations compared with a mean of only 1.03 hospitalizations among the control patients. More than 70% of the children with sickle cell anemia and gallstones had three or more hospital admissions for abdominal crises compared with 11.4% of those without gallstones. This outcome shows that the study cases were not only more likely to have abdominal crises but were also more likely to have recurrent abdominal crises ($\chi^2 = 33.02$, $df = 3$, $P < .001$).

Additionally, when reviewing the non-sickle cell conditions classified as "other," the study cases had a

significantly higher morbidity ($P < .05$) than did the control patients. This result represents a relative risk for the study cases that is 6.9 times greater than that for the control patients.

These results show that the mean number of ambulatory visits is 24.35 ± 4.81 for study cases compared with 13.41 ± 0.99 for the control patients ($t = 2.23$, $df = 84$, $P < .05$). The mean number of hospitalizations for the study cases was 10.24 ± 2.11 compared with 4.26 ± 0.50 for the control patients ($t = 2.76$, $df = 84$, $P < .05$).

DISCUSSION

These data are based on children with symptomatic sickle cell anemia and do not exclude a possible influence of "silent" gallstones.

Symptoms noted as abdominal crises were seen in 82.4% of study cases. However, only 35.3% had the right upper quadrant pain characteristic of gallbladder disease. Our results agree with those of Matthew[30] and Ariyan,[31] who reported that in patients with sickle cell anemia, abdominal crisis pain is a much more frequent manifestation of cholelithiasis than the typical right upper quadrant pain. Consequently, cholelithiasis should be included in the differential diagnosis of abdominal pain crisis of sickle cell anemia.

We disagree with the suggestion that despite the prevalence of gallstones in sickle cell anemia, symptomatic biliary tract disease is uncommon. Our study suggests that gallstones in children with sickle cell anemia may manifest early with extrabiliary symptoms during the nidus formation stage and that by the time right upper quadrant pain develops, the gallbladder mucosa is already irritated or the biliary duct system is already obstructed. This, we believe, occurs late in the pathogenesis of pigment stone formation.

Our study has also shown that children with sickle cell anemia and gallstones have higher than expected morbidity. It is important to look for stones, even in young children, when these patients present to the clinic or emergency room with recurrent acute pain. It is already too late when the stones have obstructed the bile duct and are causing biliary symptoms.

A high index of suspicion for gallstones in children with sickle cell anemia may lead to early diagnosis, which has important surgical implications. If stones are removed at age 20, the operative risk is 0.3% compared with a risk of 5% at age 45. Thus, the longer the definitive diagnosis is delayed, the greater the operative risk.

CONCLUSION

These results suggest that in children with sickle cell anemia, there is an association between the presence of gallstones and the increased incidence of morbidity. It is important that these patients be tested for gallstones as early as possible when they present to the clinic or hospital with recurrent acute pain. This novel approach to the management of these children will lead to early identification of gallstones. Subsequently, elective cholecystectomy or special cholelithotripsy[32,33] in the child with sickle cell anemia may be necessary the to reduce the high morbidity caused by cholelithiasis.

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